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Attn: Jesse Avilés
Remedial Project Manager
U.S. EPA, Region 8
Mail Code 8EPR-SR
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Denver, CO 80202-1129

Dear Mr. Avilés,

I am a resident of Denver, CO, a board member of City Park Friends and Neighbors (CPFAN) , and a member of the VB/ I 70 Superfund Site (Site) Community Advisory Group (CAG). I am the CPFAN representative to the CAG. CPFAN is a Registered Neighborhood Organization (RNO) in Denver, CO.

I submit the following comments on the U.S. Environmental Protection Agency's ("EPA") proposed intent to delete Operable Unit 1 ("OU1") of the Vasquez Boulevard and I-70 Superfund Site ("VB/I-70") from the National Priorities List ("NPL").

I endorse all of the comments, conclusions and recommendations made on the delisting of OU1 submitted by Dr. Chuck Norris, technical advisor the the CAG and the comments by Joel Minor, Esq. EarthJustice , Denver CO. I also endorse the five Recommendations made by the CAG to the EPA that were never acknowledged or responded to, by the EPA, Region 8. [1] I endorse the presentation made by Dr. Chuck Norris[2], technical advisor to the CAG in July, 2018, questioning the source of pollution in OU1.[3]

Of particular concern to me is the fact that EPA has not been able to identify the source of the pollution impacting the health and lives of people who live and work in OU1 and hence, can not offer assurance that the remedy offered by EPA, removing the top 12 inches of soil from the yards of some homes, is or will be protective of human health in the future. [4]

Delisting of OU1 should stop and the Recommendation of the CAG, delivered t the EPA Region 8, in January , 2018, should be followed:

RESOLUTION 2018-01
OF THE COMMUNITY ADVISORY GROUP VB/I70 SUPERFUND SITE

"To protect public health and the environment, the Superfund program focuses on making a visible and lasting difference in communities, ensuring that people can live

and work in healthy, vibrant places." https://www.epa.gov/superfund

In July 2018, the Community Advisory Group (CAG) was briefed by Dr. Chuck Norris regarding the shortcomings of the Remedial Investigation for Operable Unit 1, and Health Assessment for Operable Unit 1 of the VB/I70 Superfund Sites: (https://drive.google.com/file/d/1X9XGpfXNiKVt22ydq99ydq2f0WjbVdKf/view?usp=sharing)

The presentation demonstrated that both the Remedial Investigation and the Health Assessment were based on inconclusive evidence and an incomplete understanding regarding the source and placement and extent of soil contamination.

Absent this crucial information, the choice of remedy subsequently chosen for Operable Unit 1 was, at best, a shot in the dark and there was no way for EPA Region 8 to be able to predict the risk to people living in OU1, from even the two contaminants of concern, arsenic and lead, identified by EPA.

The Community Advisory Group (CAG) recommended that EPA:

** Re-open its investigation of the source(s) of contamination documented in the VB/I70 Superfund Site soils*

** Expand its assessment of contamination of affected soils, groundwater, air by redefining Operable Unit 1, or establishing a new Operable Unit*

** Halt the delisting process for Operable Unit 1*

** Honor the Environmental Justice designation given by the EPA to the VB/I70 Superfund Site by investigating the disproportionate environmental impacts from all sources – including industry, other Superfund sites, and major transportation corridors.*

NEW INFORMATION shows that the obsolete method used by EPA to evaluate risk of contaminants of concern, arsenic and lead, to people who live and work in OU1, is no longer valid and, in fact, poses great health risk to generations of humans and wildlife exposed to

these and the many other Endocrine Disruptors (ED) 's found in OU1, that have been ignored by EPA Region 8.[5]

The EPA BASELINE HUMAN HEALTH RISK ASSESSMENT (BHHRA) was issued in 8/1/2001, the FINAL REMEDIAL INVESTIGATION REPORT OPERABLE UNIT 1 (FRIR) in July 1, 2001 and the VASQUEZ BLVD. I-70 RECORD OF DECISION (ROD) OPERABLE UNIT 1 RESIDENTIAL SOILS in July 25, 2003.

Arsenic and lead were identified as contaminants of concern in OU1.

Arsenic and lead, metals, have been identified as endocrine disruptors (ED) [67].

An endocrine disruptor is defined by the Endocrine Society as: : "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action"

Since 2001 when EPA issued the BHHRA and FRIR, science has made tremendous advances in understanding the impacts of exposure to EDs on a range of behavioral, endocrine and neurobiological problems in humans.[8]

"As the global scientific and medical community continues to express concern over EDCs and their harmful effects on human health, public policies should be grounded in the latest available scientific evidence."[9]

These effects not only manifest in the person originally exposed to the ED but can extend to their offspring and the offspring of their children.[10]

The old toxicological method of a single- exposure, dose-response used by the EPA has been found to no longer be valid or useful to understand the health impacts of ED on humans as even the tiniest dose can have a huge impact, even more than a larger does, depending on the stage of development. [11]

Also missing from the EPA risk assessment model are the impacts of combinations of compounds on humans at various stages of development in their lives. [12]

In view of the fact that EPA Region 8 used obsolete methodologies to evaluate the impact and risks of exposure of arsenic and lead on human health EPA's efforts to delist OU1 at this time are premature and are not protective of human health.

The Site was first added to the USEPA NPL in January, 1999 and divided up into 3 Operating Units, OU1,OU2 and OU3. OU1 consisted solely of residential units and excluded the many commercial and public areas in OU1 such as streets.

The BASELINE HUMAN HEALTH RISK ASSESSMENT was issued in 8/1/2001, the FINAL REMEDIAL INVESTIGATION REPORT OPERABLE UNIT 1 in July 1, 2001 and the VASQUEZ BLVD. I-70 RECORD OF DECISION (ROD) OPERABLE UNIT 1 RESIDENTIAL SOILS in July 25, 2003.

Arsenic and lead, two potent Endocrine Disruptors were identified as as contaminants of concern. EPA chose to ignore the many other contaminants that have been identified in OU1 in other reports done by CDOT[13] and Pinyon[14] [15]:

The CDOT report lists some of the pollutants found in OU1:

benzene
toluene
ethylbenzene
xylene
Semi-volatile organic compounds
paraffins
bio-organic compounds.
Perchlorethylene
Diesel-range hydrocarbons
cadmium
chromium
lead
mercury

This is apparently just the tip of the ice berg of the chemical and metal contaminants and EDs found in OU1 that EPA Region 8 has chosen to ignore even over the repeated requests of members of the Environmental Justice neighborhood in OU1, to expand the EPA investigation of toxic pollution that is making them sick and shortening their lives.[16]

For example, community concerns taken form the EPA Community Involvement Plan, :

EPA may not be addressing all possible contamination in the area. EPA should consider past industrial and commercial uses that included a possible landfill.
EPA may not be drilling enough wells to get a complete picture as groundwater flows in all different directions.
• EPA should expand investigation because future development on and off site will be impacted by contaminants that EPA does not address now.[17]

I recommend that the EPA Region 8 :

(1) Abandon its attempt to delist OU1 from the Site;

(2) Immediately commence testing the soil and water in OU1, at many locations, elevations and depths, with special emphasis at identifying "hot spots", sufficient to ascertain the source of the arsenic and lead pollution in OU1;

(3) Identify all pollutants and their sources in OU1 and devise a plan to eliminate them for this Environmental Justice community;

(4) Include the CAG fully as representatives of the community, in he CERCLA process for example by EPA attending CAG meetings and providing services as outlined in the EPA Superfund Community Involvement Handbook[18] ;

(5) Hold well advertised, formal pubic hearings in the community, to inform residents of the health and safety risks associated with living and working in a Superfund Site and to let EPA, CDPHE and Denver officials hear, freely, first hand , the concerns and ideas of residents of affected neighborhoods. "Drop ins" to not achieve this purpose;

(6) Foster a congenial, welcoming attitude toward the community and toward the CAG;

(7) Provide requested documents to the CAG in a timely fashion;

(8) Comply with EPA regulations regarding public assess to documents and records at specified locations near OU1. This requirement has been blatantly ignored by EPA , Region 8;

(9) Respond to CAG Resolutions in a timely fashion so that the CAG may be a part of the CERCLA process as prescribed by law, before actions are taken by EPA Region 8, that will impact the community; and,

(10) If OU1 is delisted, immediately set up a new OU4 to carry out the steps necessary to protect the health and safety of residents in OU1 who live in these Environmental Justice neighborhoods.

The following excerpts are taken from Introduction to Endocrine Disrupting Chemicals (EDC), a Guide for Public Interest Organizations and Policy Makers:[19]

EXECUTIVE SUMMARY

Scientific knowledge about endocrine-disrupting chemicals (EDCs) has been increasing rapidly in recent years. Along with evidence on the impact of these chemicals on human health, there is a growing body of literature that suggests that relying upon traditional scientific methods for assessing the human health impact of chemicals is inadequate when assessing EDCs and such methods, in fact, may result in dangerous and faulty policy. EDCs are defined by the Endocrine Society as: "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action." Hormones are natural chemicals produced in cells within endocrine glands, which are located throughout the body. Hormones coordinate the development of every individual from a single fertilized cell to the many millions of specialized cells that make up the blood, bones, brain, and other tissues. More than a century of biological research has proven that as an individual develops, the changing hormonal needs of each organ require hormones to be present in precise amounts at particular times, and that the needs of each organ and tissue change through the life cycle. Circulating in very low concentrations, hormones regulate the body's response to different nutritional demands (e.g. hunger, starvation, obesity, etc.); they are critical to reproductive function; and they are essential to normal development of the body and brain. As a whole, the endocrine system is one of the body's major interfaces with the environment, allowing for development, adaptation and maintenance of bodily processes and health. In other words, they play key roles in determining the quality of life, and many hormones are absolutely essential for survival. Because of the endocrine system's critical role in so many important biological and physiological functions, impairments in any part of the endocrine system can lead to disease or even death. By interfering with the body's endocrine systems, EDC exposure can therefore perturb many functions. EDCs are a global and ubiquitous problem. Exposure occurs at home, in the office, on the farm, in the air we breathe, the food we eat, and the water we drink. Of the hundreds of thousands of manufactured chemicals, it is estimated that about 1000 may have endocrine-acting properties. Biomonitoring (measurement of chemicals in body fluids and tissues) shows nearly 100% of humans have a chemical body burden based on detectable levels in blood, urine, placenta and 2 umbilical cord blood, and body tissues such as adipose tissue (fat). Some common examples of EDCs include DDT and other pesticides; bisphenol A (BPA) and phthalates used in children's products, personal care products and food containers; and flame retardants used in furniture and floor coverings. In addition to the known EDCs, there are countless suspected EDCs or chemicals that have never been tested. Exposures to known EDCs are relatively high in contaminated environments in which industrial chemicals leach into soil and water; are taken up by microorganisms, algae, and plants; and move into the animal kingdom as animals eat the plants, and bigger animals eat the smaller animals. Animals at the top of the food chain, including humans, have the highest concentrations of such

environmental chemicals in their tissues. There is good reason to suspect that increasing chemical production and use is related to the growing incidence of endocrine-associated pediatric disorders over the past 20 years, including male reproductive problems (cryptorchidism, hypospadias, testicular cancer), early female puberty, leukemia, brain cancer, and neurobehavioral disorders. At the same time, the global production of plastics grew from 50 million tons in the mid-1970s to nearly 300 million today, and sales for the global chemical industry have sharply increased from USD$171 billion in 1970 to over USD$4 trillion in 2013. Chemicals such as polychlorinated biphenyls (PCBs), BPA, and phthalates, are now detectable in serum, fat, and umbilical cord blood in humans around the globe. In fact, the concept of "better living through chemistry" was introduced by the chemical industry in the 1930s. This pervasive notion underlies the global escalation in chemicals production. Over the last two decades there has been burgeoning scientific evidence based on field research in wildlife species, epidemiological data on humans, and laboratory research with cell cultures and animal models that provides insights into how EDCs cause biological changes, and how that may lead to disease. However, endocrinologists now believe that a shift away from traditional toxicity testing is needed. The prevailing dogma applied to chemical risk assessment is that "the dose makes the poison." These testing protocols are based on the idea that there is always a simple, linear relationship between dose and toxicity, with higher doses being more toxic, and lower doses less toxic. This strategy is used to establish a dose below which a chemical is considered "safe," and experiments are conducted to determine that threshold for safety. Traditional testing involves chemicals being tested one at a time on adult animals, and they are presumed safe if they did not result in cancer or death. A paradigm shift away from this dogma is required in order to assess fully the impact of EDCs and to protect human health. Like natural hormones, EDCs Introduction to EDCs (December 2014) 3 exist in the body in combination due to prolonged or continual environmental exposures. Also like natural hormones, EDCs have effects at extremely low doses (typically in the part-per-trillion to part-per-billion range) to regulate bodily functions. This concept is particularly important in considering that exposures start in the womb and continue throughout the life cycle. A new type of testing is needed in order to reflect that EDCs impact human health even at the low levels encountered in everyday life. Rather than the old toxicological method of a single-exposure, dose-response approach using pure compounds, it is vital that new risk assessment procedures simulate more closely what occurs in nature. Rather than pure compounds, we need to know the effects of combinations of compounds or mixtures. We also need to recognize that because certain life stages are particularly vulnerable to EDCs, especially early in development, testing EDC effects on adults, which is the norm in traditional risk assessment, may not extrapolate to the exposed fetus or infant.

2. INTRODUCTION TO THE HUMAN ENDOCRINE SYSTEM AND EDCs

I. BACKGROUND ON THE HUMAN ENDOCRINE SYSTEM The endocrine system consists of a series of glands that are distributed throughout the body (Figure 1). Each gland produces one or more hormones. Hormones are natural chemicals that are produced in cells within a gland and released into the circulatory system, where they travel through the bloodstream until they reach a target tissue or organ. There, they bind to specific receptors, triggering a response such as production of another hormone, a change in metabolism, a Figure 1. Diagram of major endocrine glands in the human body, shown in a female (left) and male (right). 8 behavioral response, or other responses, depending upon the specific hormone and its target. Some endocrine glands produce a single hormone, while others produce multiple endocrine hormones (Table 1). For example, the parathyroid gland produces a single known hormone (parathyroid hormone), whereas the pituitary gland makes eight or more hormones, including prolactin and growth hormone. Prolactin is involved in making breast milk, and it is only synthesized and released from the pituitary glands of women who are breast feeding their infants. By contrast, growth hormone is synthesized throughout life, as it is important for growth and development in childhood and for building and maintaining muscles and the skeleton in adulthood. It is also notable that some endocrine glands have other, non-endocrine functions. The pancreas is a good example: it produces the hormone insulin, which circulates in the blood and is necessary for normal regulation of blood sugar levels; and it makes digestive enzymes that go directly to the digestive tract and are not part of the endocrine system because they are not released into the blood. Clearly, endocrine systems and functions are complex and diverse, with each gland and hormone playing unique roles in health and well-being. These examples, together with the additional information provided in Table 1, underscore a critical point about all endocrine systems: they are absolutely necessary for human health. Endocrine glands and the hormones they produce enable the body to adapt to environmental change; they allow metabolic adjustments to occur in response to different nutritional demands (e.g. hunger, starvation, obesity, etc.); they are critical to reproductive function; and they are essential to normal development of the body and brain. Thus, as a whole, the endocrine system is one of the body's major interfaces with the environment, allowing for development, adaptation, and maintenance of bodily processes and health. Because of the endocrine system's critical role in so many important biological and physiological functions, impairments in any part of the endocrine system can lead to disease or even death. For example, diabetics have deficiencies in insulin release and/or action, and people with type I diabetes will die without insulin replacement. Aldosterone is also critical for life, and adrenal diseases affecting aldosterone function can be life-threatening. Often, under- or over-secretion of hormones such as thyroid hormone results in metabolic disturbances and many physical and neurobiological changes, due to thyroid hormone's key role in day-to-day cellular metabolism and brain function. Other hormonal dysfunctions include infertility, growth disturbances, sleep disorders, and many other chronic and acute diseases. Thus, endocrine hormones must be released at the appropriate amounts, and

endocrine glands must be able to adjust hormone release in response to the changing environment, to enable a healthy life.

II. WHAT ARE EDCs, HOW ARE THEY USED, AND WHERE ARE THEY FOUND? EDCs were recently defined by the Endocrine Society (endocrine.org), the largest international group of scientists and physicians working and practicing in the field of endocrinology, as: "an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action" (5). There are over 85,000 manufactured chemicals, of which thousands may be EDCs. A short list of representative EDCs and their applications is provided in Table 2. There are dozens of other processes and products that include EDCs, too numerous to include in this table. TABLE 2. SOME KNOWN EDCS AND THEIR USES Category/Use Example EDCs Pesticides DDT, chlorpyrifos, atrazine, 2,4-D, glyphosate Children's products Lead, phthalates, cadmium Food contact materials BPA, phthalates, phenol Electronics and Building materials Brominated flame retardants, PCBs Personal care products, medical tubing Phthalates Antibacterials Triclosan Textiles, clothing Perfluorochemicals Abbreviations: BPA: bisphenol A; 2,4-D: 2,4-dichlorophenoxyacetic acid; DDT: dichlorodiphenyltrichloroethane; PCBs: polychlorinated biphenyls People and animals come into contact with EDCs by a variety of routes (Table 3), including consumption of food and water, through the skin, by inhalation, and by transfer from mother to fetus (across the placenta) or mother to infant (via lactation) if a woman has EDCs in her body. Introduction to EDCs (December 2014)

To understand how EDCs perturb the endocrine system, it is necessary to have some basic understanding of how natural hormones work in the body. The chemical composition and three-dimensional shape of each endocrine hormone is unique. Every hormone in turn has a corresponding receptor (or receptors) localized on the target cells. A receptor's shape is complementary to its hormone, similar to the way in which one key (hormone) is specific to a lock (receptor). The response of a given tissue or organ to a hormone is determined by the presence of receptors on target cells and receptor activation by hormone binding. The ability of a hormone to activate its receptor depends upon several factors, including how much hormone is synthesized and released by the endocrine gland, how it is transported through the circulation, how much reaches the target organ, and how potently and for how long the hormone can activate its receptor. These properties Introduction to EDCs (December 2014) 13 are fundamental to normal hormonal signalling. EDCs can interfere with any – and all – of these steps. EDCs often disrupt endocrine systems by mimicking or blocking a natural hormone. In the case of hormone mimics, an EDC can "trick" that hormone's receptor into thinking that the EDC is the hormone, and this can inappropriately activate the receptor and trigger processes normally activated only by a natural hormone. In the case of hormone blockers, an EDC can bind to a hormone's receptor, but in this case, the receptor is blocked and cannot be activated, even if the natural

hormone is present. The best known example is endocrine disruption of estrogenic hormones, which act upon the body's estrogen receptors (ERs). In both males and females, ERs are present in many cells in the brain, in bone, in vascular tissues, and in reproductive tissues. While estrogens are best understood for their roles in female reproduction, they are important for male reproduction, and are also involved in neurobiological functions, bone development and maintenance, cardiovascular functions, and many other functions. Natural estrogens exert these actions, after being released from the gonad (ovary-female or testis-male), by binding to ERs in the target tissues. Estrogen receptors are not the only receptors that are attacked in this manner by EDCs, although they are the best studied. Receptors for androgens (testosterone), progesterone, thyroid hormones, and many others, are interfered in their functioning by EDCs. In addition, because EDCs are not natural hormones, a single EDC may have the ability to affect multiple hormonal signalling pathways. Thus, it is quite likely that one type of EDC can disrupt two, three, or more endocrine functions, with widespread consequences on the biological processes that are controlled by those vulnerable endocrine glands. 14 3.

IMPACT of ED

3. IMPACTS OF EDCs I. HISTORICAL PERSPECTIVE ON EDCs Since 1940 there has been an exponential increase in the number, and abundance, of manufactured chemicals, some of which have been released (intentionally or not) into the environment. This chemical revolution has irreversibly changed ecosystems in a manner that has had severe impacts on wildlife and human health. Rachel Carson's book Silent Spring, published in 1962, was the first public warning that environmental contamination, in particular the pesticide DDT, might be responsible for the reduced numbers of birds due to reproductive failure caused by this and other toxic chemicals. However, whether chemical exposures caused toxicity in humans was unclear, with the exception of massive chemical spills or contamination. In addition, although it is now well-accepted that some chemicals and pharmaceuticals can cross the placenta, fifty years ago it was thought that the placenta acted as a barrier, protecting the developing fetus from any exposure. Two unfortunate clinical events transformed and ultimately negated this perspective. The first was the realization that pregnant women given thalidomide to alleviate nausea during the first trimester sometimes gave birth to infants with severe malformations. Clearly, the fetus was vulnerable to pharmaceuticals given to the mother. The second breakthrough discovery was that of diesthylstilbestrol (DES) given to pregnant women to avert miscarriage. DES is similar in its properties to natural estrogen hormones. Girls who had been exposed to DES in the womb often had reproductive tract malformations and some developed rare reproductive cancers in adolescence that were normally only seen in postmenopausal women (6). Because of the long latency between exposure (fetus) and disease (adolescence), the connection to DES was not initially obvious. However, experimental work in mice exposed with DES as fetuses also demonstrated reproductive disorders in the offspring as they matured to adulthood. This cause-

and-effect relationship between fetal DES, reproductive tract malformations, and cancer later in life in girls was tied together to experimental DES effects in mice, and the field of endocrine disruption was born. Meanwhile, wild American alligators in Florida exposed to dicofol, an organochlorine pesticide chemically related to DDT, exhibited genital and reproductive malformations. The discovery of deformed frogs in Minnesota (US) by school children on a nature field trip further illuminated the problem of chronic pollution by agricultural runoff. Many other examples of associations between these and other EDCs have since been confirmed in wildlife of every class (7). Introduction to EDCs (December 2014) 15 Not surprisingly, chemical contamination of the environment has been proven to affect humans and further discussion of this will be provided below. But the most direct evidence for cause and effect came from several large-scale disasters in which humans were exposed to varying amounts of chemicals, including both high levels, which were acutely toxic, and lower levels, which have now been shown to cause more chronic, subtle, and long-lasting effects. One example is the explosion of a chemical manufacturing plant in Seveso, Italy, that exposed residents to high levels of dioxins. Two more tragic exposure examples are Yusho in Japan (PCBs), and Yucheng in Taiwan (polychlorinated dibenzofurans) in which contaminated cooking oil caused mass poisoning. Of recent concern is the poisoning of schoolchildren in India in July 2013 through oil contaminated with the organophosphate pesticide monocrotophos, which resulted in 23 deaths. The long-term endocrinedisrupting effects of monocrotophos remain to be seen, although there is evidence of estrogenicity from studies on mice and fish (8, 9). Another common route of human exposure is in agriculture with the routine seasonal spraying of crops with pesticides. This established practice can create a body burden that affects exposed workers, nearby residents, consumers of the food, and even future generations, as described below. When humans are tested for the presence of EDCs in their blood, fat, urine, and other tissues, the results consistently demonstrate a variety of EDCs in all individuals worldwide. 16 I

EDC EXPOSURES TO THE INDIVIDUAL, AND TO FUTURE GENERATIONS Exposure to environmental chemicals is life-long. Animals and humans living in contaminated environments carry personal body burdens – the amount of chemicals contained in an individual's tissues – from direct exposure accumulated throughout their lives. Some of these EDCs are persistent and bioaccumulative (i.e., build up over time in body tissues). When humans are tested for the presence of EDCs in their blood, fat, urine, and other tissues, the results consistently demonstrate a variety of EDCs in all individuals worldwide. These measurements reflect contact with EDCs through food, water, skin absorption, and from the atmosphere. Fat is a particularly important reservoir for EDCs, as these chemicals' compositions tend to make them fat-soluble. In addition, measures of EDC body burdens reflect not only contemporary contact with EDCs; they also include past exposures, sometimes decades ago, to persistent chemicals such as PCBs and others. Beyond an individual's own lifetime of exposures is the inheritance of exposures to EDCs from

his/her ancestors. For example, during pregnancy, some of the chemicals stored in a woman's body fat may cross the placenta and affect her developing embryo. Some EDCs are detectable in breast milk and can be passed to the suckling infant. In addition, there is now evidence that EDCs induce changes to germ cells – precursors to sperm and egg cells – making their effects heritable not just to one's own children, but also to grandchildren, great-grandchildren, and beyond. In other words, children can inherit the negative consequences induced by the exposures of their ancestors. This is very important, because it underscores the point that the introduction of a chemical into the environment, if it affects the germ cells, will be inherited long after the chemical is cleaned up or breaks down. III.

EDCs AND ENDOCRINE DISEASE It has been estimated that, globally, upwards of 24% of human diseases and disorders are attributable to environmental factors (10) and that the environment plays a role in 80% of the most deadly diseases, including cancer and respiratory and cardiovascular diseases (11). Because perturbation of the endocrine system is fundamental to the most prevalent of these diseases, EDCs may be primary contributors. The incidence of endocrine-associated pediatric disorders, including male reproductive problems (cryptorchidism, hypospadias, testicular cancer), early female puberty, leukemia, brain cancer, and neurobehavioral disorders, have all risen rapidly over the past 20 years. The prevalence of developmental disability in US children increased from 12.84% to 15.04% between 1997-2008 (12). The preterm birth rate in the US, UK and Scandinavia has increased by more than 30% since 1981, an outcome associated with increased rates of neurological Introduction to EDCs (December 2014) 17 disorders, respiratory conditions and childhood mortality, as well as obesity, type 2 diabetes, and cardiovascular disease in adulthood. Data from human, animal, and cell-based studies have generated considerable evidence linking EDC exposure to these and other human health disorders. The increased endocrine disease rates parallels increased production of manufactured chemicals. Global production of plastics grew from 50 million tons in the mid-1970s to nearly 300 million tons today. Similar trends hold for other chemical sources including pesticides, fire retardants, solvents, and surfactants. Sales for the global chemical industry have sharply increased from USD$171 billion in 1970 to over USD$4 trillion in 2013 (13). These and other chemicals such as PCBs, BPA, and phthalates, are detectable in human serum, fat, and umbilical cord blood (14-16). While associations between increased human chemical exposures and increased disease rates are suggestive they do not 'prove' that the two are linked. Data from cell-based studies, animal studies, and other experimental systems over the past few decades, however, have provided a wealth of evidence supporting this direct link. Proving a chemical contributes to a human disease would require exposing a group of humans and then observing the resulting disorder. Though this type of testing is done for pharmaceuticals, it would be unethical and impossible for testing the impact of toxicants on humans. Conclusions about EDC-related health effects, therefore, have to be made using data

from epidemiology studies, which can only reveal associations, and by making inferences about human risk from experimental data obtained from animals or cell-based models. An additional challenge is that humans are exposed to a complex mixture of chemicals across the lifespan, making it difficult to establish if health effects result from exposure to a few problematic chemicals or a collective combination of chemicals. Thus, although environmental exposures are recognized to contribute to endocrine-related disorders, finding a 'smoking gun' linking any specific EDC to any specific disease is difficult. THE PRETERM BIRTH RATE IN THE US, UK AND SCANDINAVIA HAS INCREASED BY MORE THAN 30% SINCE 1981, AN OUTCOME ASSOCIATED WITH INCREASED RATES OF NEUROLOGICAL DISORDERS, RESPIRATORY CONDITIONS AND CHILDHOOD MORTALITY, AS WELL AS OBESITY, TYPE 2 DIABETES, AND CARDIOVASCULAR DISEASE IN ADULTHOOD. 18 In many ways, the present debate about EDCs parallels the long and contentious debate surrounding the risks of smoking. Tobacco smoke was first shown to cause lung cancer in 1950, but debate about this link and how to regulate tobacco raged for decades, with executives from the biggest tobacco companies famously testifying before the US Congress in 1994 that the evidence showing cigarette smoking caused diseases such as cancer and heart disease was inconclusive. Today smoking remains the single biggest cause of cancer in the world and kills one person every 15 minutes (17). For EDCs the available data linking chemicals or a class of chemicals to chronic disease is, in some cases, comparable in strength and breadth to the evidence linking smoking with lung cancer. Thus, despite the insistence by some groups that the evidence is inconclusive, the body of data revealing EDC-related health effects is sufficient to warrant concern that EDCs adversely impact public health.

NEUROLOGICAL AND BEHAVIORAL DISORDERS Numerous public health agencies including the World Health Organization, the United Nations, and the National Toxicology Program in the US have expressed concern about EDC effects on the brain and behavior (18, 19). Childhood neuropsychiatric disorders are increasing in prevalence with as many as 1 in 6 children in the US now diagnosed with at least one (12). These disorders include attention deficit hyperactivity disorder (ADHD) and Autism Spectrum Disorder (ASD), as well as depression and other mood disorders, learning disabilities, executive function deficits, and conduct disorders. As a class, PCBs have the strongest and longest-known associations with neurological disorders. In humans, there is evidence for impaired neurodevelopment (20, 21), lower IQ, and problems with attention, memory, and fine motor skills such as writing. Some of these studies were completed in communities living near the Arctic, a place long thought to be pristine but now known to bioconcentrate PCBs and other persistent pollutants to some of the highest levels on the planet (22). Some PCB metabolites alter thyroid activity, long recognized to elevate risk of impaired neural development. Similarly, polybrominated diphenyl ethers (PBDEs) are associated with reduced IQ, and other cognitive deficits (23). PBDEs affect neurotransmitter activity, synaptic

organization, and neuron viability suggesting CHILDHOOD NEUROPSYCHIATRIC DISORDERS INCLUDE DEPRESSION, MOOD DISORDERS, LEARNING DISABILITIES, EXECUTIVE FUNCTION DEFICITS, AND CONDUCT DISORDERS. that they impact not only brain development but also brain aging. Links have been reported between pesticide exposures and neurodegenerative disorders such as Parkinson's Disease (24) and with depressive behaviors (25). Brominated flame retardants, perfluorinated compounds, and pesticides (organophosphates such as chlorpyrifos and organochlorines), are linked to ADHD, ASD, and related learning disabilities (26), but the evidence remains inconclusive. Experimental animal data show numerous neurobiological changes caused by EDCs, including neuronal development, properties of synaptic organization, neurotransmitter synthesis and release, and structural organizational effects on the developing brain. In conjunction with a growing literature on behavioral effects of EDC exposures, especially during development, these studies underscore the brain as a vulnerable target of EDCs (27).

OBESITY, METABOLIC DYSFUNCTION AND RELATED DISORDERS Obesity rates are rising rapidly globally. While lifestyle factors such as diet and activity level are clearly primary contributors, accumulating evidence suggests that other factors, including chemical exposures, may also be playing a role. Chemicals referred to as "obesogens" are thought to enhance weight gain by altering or Chemicals referred to as "obesogens" are thought to enhance weight gain by altering or reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes. 20 reprogramming key parts of the endocrine system governing metabolism, energy balance, and appetite, resulting in obesity and its related adverse health outcomes (28-31). Laboratory animal work shows that developmental exposure is particularly effective in predisposing an individual to weight gain and subsequent related adverse health outcomes including type-2 diabetes, cardiovascular disease, altered lipid metabolism and altered glucose sensitivity (32-34). The most well studied obesogenic EDCs to date are tributyltin (TBT) and triphenyltin (TPT) (30); these and other chemicals act through hormone receptors called PPARγ (34). Disruption of thyroid hormone function is another mechanism by which obesogenic chemicals can act, due to the thyroid gland's important role in normal maintenance of metabolism. Some effects of PCBs and PBDEs may be mediated via the thyroid axis (35, 36). A brominated flame retardant, Firemaster 550, was shown to alter thyroid hormone levels in pregnant rats and their offspring, with the pups growing up to develop obesity, cardiac disease, early puberty and insulin resistance (37). Although that work needs to be repeated and extended, it is noteworthy that Firemaster 550 is now one of the most commonly used fire retardants in the US; it is a ubiquitous contaminant of household dust, and biomonitoring studies have identified Firemaster 550 in human urine (38). Although the field of environmental obesogens is relatively new, phthalates, perfluorinated

compounds, BPA, dioxins, and some pesticides are emerging as potential obesogens, meriting further study.

REPRODUCTIVE DISORDERS Among the strongest associations between EDC exposures and adverse outcomes are those for reproductive development, physiology, and pathology. The increased prevalence over the past 50 years of hormone-sensitive cancers (e.g. breast, prostate), compromised fertility, early puberty, decreased sperm counts, genital malformations, and unbalanced sex ratios (39) are at least partially attributable to increased chemical abundance and exposures. The increase in early puberty in girls, while contributed to by many factors including nutrition, stress, and ethnicity, may in part be due to exposures to estrogenic EDCs (40, 41). Such estrogenic compounds are also associated with uterine fibroids, ovarian dysfunction, and subfertility in humans and in animal models (39, 42, 43). BPA is linked with reduced egg quality and other aspects of egg viability in patients seeking fertility treatment (44, 45) – effects which closely parallel those seen in animal models (46). Danish women under 40 working in the plastics industry were more likely to have sought fertility assistance than unexposed women of the same age (47). In men, sperm counts have declined as much as 50% over the last half century in certain regions (48, 49). Several chemicals, most notably phthalates, are associated with a variety Introduction to EDCs (December 2014) 21 of adverse effects on the male urogenital tract, including cryptorchidism, hypospadias, prostate disease and testicular cancer (50). CANCER Like other complex diseases, most cancers result from the interplay of genetic predisposition and the environment encountered by the individual. Relatively few cancers are linked to a single gene, underscoring the key role played by the environment. In fact, 2 in 3 cancer cases are environmentally-linked in some way, leading the American Cancer Society to conclude that most cancers are preventable with lifestyle changes such as improved diet, more exercise, and reduced smoking. Certain jobs are associated with an elevated risk of cancers, particularly those with high burdens of chemical exposure, including painting, fire-fighting, working in the coal, steel, or rubber industries, textile and paper manufacturing, and mining. The list of known chemical carcinogens is long and includes metals, vinyl chloride, benzidine (used in dyes), solvents such as benzene, polycyclic aromatic hydroConsidering how many cancers involve hormones, such as prostate, breast, uterine, and other reproductive tissues, it may not be surprising that estrogenic and other hormoneactive chemicals such as BPA, phthalates and some pesticides, are thought to contribute to carcinogenic risk. 22 carbons (PAHs), dioxins, fibers and dust (silica, asbestos, etc.), some pesticides including those on the Stockholm Convention's list of Persistent Organic Pollutants, and numerous pharmaceuticals including the synthetic estrogens. Some (although not all) of these chemicals are EDCs. Considering how many cancers involve hormones, such as prostate, breast, uterine, and other reproductive tissues, it may not be surprising that estrogenic and other hormone-active chemicals such as BPA, phthalates and some pesticides, are thought to contribute to carcinogenic risk (51, 52). The question of which EDCs have the greatest impact,

and when in life (prenatal, childhood, adult) EDC exposure most significantly contributes to cancer risk, remain unresolved issues. Studies using cellular and animal models have revealed that early life exposure to chemicals such as BPA, phthalates, perflourinated compounds, PCBs, and some pesticides can heighten cancer risk later in life (52). Emerging epidemiological studies are beginning to establish correlative relationships in humans (53). Establishing such links in humans is difficult because it requires having information about exposures that may have occurred years or even decades earlier. There is no question, however, that based on the critical and broad effects of the environment on cancer prevalence and manifestation, minimizing chemical exposures will have a tremendous positive impact on cancer risk and probability of survival.

OTHER DISEASES AND DISORDERS Animal work and epidemiological studies in humans indicate that EDC exposure contributes to other health conditions including cardiovascular disease and diabetes. A new frontier in research is the immune and inflammatory effects of EDCs. Inflammation is associated with a wide range of chronic diseases including obesity, cognitive deficits, cardiovascular disease, respiratory disorders, cancer, and even autism. The immune and endocrine systems often work together in responding to environmental challenges, and the convergence of their signaling pathways may underlie some of the inflammatory effects.

TRADITIONAL CONCEPTS IN CHEMICAL TESTING AND WHY THEY ARE INADEQUATE TO DETERMINE ENDOCRINE-DISRUPTING ACTIVITY. Traditional Approach to Chemical Testing: 'The Dose is the Poison' Why this approach is insufficient for Endocrine-Disrupting Chemicals Tests individual chemicals one at a time Every person in the world now carries a body burden of chemicals that did not exist before 1940. Many more are being produced and released into the environment each year. Testing chemicals one at a time can't keep pace with exposure and doesn't take into account how combinations of chemicals within the body are impacting human development or health. Assumes individual chemicals have a "safe or acceptable" level of exposure below which there are no adverse effects The endocrine system regulates virtually every aspect of human health from development in the womb, to growth, to reproduction, and overall health. Recent science shows that even very small amounts of these chemicals or mixtures of these chemicals disrupt the endocrine system, reducing intelligence, disrupting reproductive systems, and causing other health problems. There may, in fact, be no safe level, especially when individuals have hundreds of these chemicals in their bodies. Tests are focused on adult animals Hormones regulate body systems beginning in the womb and throughout life. Tests conducted only on adult animals can't capture the impact of chemicals on the endocrine system throughout the body's life cycle. Presumes doses below the amounts which cause test animals to die or develop a target disease (usually cancer) are 'safe' Endocrine-disrupting chemicals have many impacts beyond death or disease.

4. RECENT ADVANCES IN THE SCIENCE OF EDCs, AND THE NEED FOR A NEW SCIENTIFIC PARADIGM TO EVALUATE EDC RISK There is widespread, conclusive agreement about the hazards posed by cigarette smoke, lead, radioactive materials, and many chemicals. Decades of laboratory research, together with clinical evidence in individuals and epidemiological data from human populations, have provided conclusive evidence for cause-and-effect links between exposure and disease or death. In the case of chemical assessment and management, the ability to directly link an exposure to an adverse health outcome, or death, can be proven in cases of known exposures to high levels of a particular chemical. For example, the large-scale examples described earlier of industrial contamination (Seveso) and cooking oil (Yusho, Yucheng) resulted in severe birth defects and neurocognitive impairments in children born to women who, while pregnant, consumed the contaminated oil or were directly exposed to dioxins. Thus, traditional toxicological testing has been very important in identifying and characterizing such chemicals that pose a threat to humans and wildlife. However, because most people are exposed to a variety of EDCs, usually at low doses, in mixtures, and at different life stages, the ability to directly relate a disease in adulthood – for example, type 2 diabetes – to exposures to EDCs during life, especially during critical developmental periods, is much more difficult. The following sections describe how a new way of thinking is needed to properly understand effects of EDC exposures and their long-term manifestations as impaired quality of life, chronic disease, and cancers (Table 4). An additional brief summary of these concepts is provided at the end of this section (Box 2). Introduction to EDCs (December 2014) 25 I.

THE NEED FOR A PARADIGM SHIFT TO MOVE OUR SCIENTIFIC UNDERSTANDING OF EDCs FORWARD The Chemical Revolution was accompanied by environmental contamination leading to cancers, heavy metal poisoning, and air and water pollution. This in turn led to the need for testing to create general safety standards. Toxicological testing of pure chemicals at varying dosages successfully flagged certain chemicals in the environment that caused overt toxicity, cancers, and death. Based on information from dose-response curves, efforts were made to determine a threshold below which exposures did not result in any obvious acute toxicity, and to use this information to extrapolate downwards to establish a 'safe' level of exposure. We now know that the type of testing and the range of doses used in standard toxicological risk assessment are often inaccurate when applied to EDCs (54). The 'old science' approach makes several assumptions and is based on testing protocols that are not realistic. For example, most testing is performed in adult animals (e.g. We now know that direct exposures of an individual to EDCs cause a range of behavioral, endocrine, and neurobiological problems. This requires a paradigm shift in how to conduct risk assessment. 26 rats) using acute exposures to a single chemical. However, all humans and animals are exposed to a variety of EDCs in varying levels and mixtures throughout their lives. Thus, while the traditional toxicological

methods can be useful, they must be transcended in identifying EDCs and determining their consequences. Over the last two decades there has been burgeoning scientific evidence based on field research in wildlife species, epidemiological data on humans, and laboratory research with animal models, providing insights into how EDCs cause biological changes, and how that may lead to disease. We now know that direct exposures of an individual to EDCs cause a range of behavioral, endocrine, and neurobiological problems. This requires a paradigm shift in how to conduct risk assessment. For example, rather than the old toxicological method of a single-exposure, doseresponse approach using pure compounds, it is vital that new risk assessment procedures simulate more closely what occurs in nature. Rather than single compounds, we need to know the effects of combinations of compounds or mixtures. We also need to recognize that because certain life stages are particularly vulnerable to EDCs, especially early in development, that testing EDCs in adults may not extrapolate to the exposed fetus or infant. We will elaborate upon these concepts below.

I. DEVELOPMENTAL EXPOSURE AND WINDOWS OF VULNERABILITY Hormones coordinate the development of every individual, from a single fertilized cell to the many millions of specialized cells that make up the blood, bones, brain, and other tissues. These endogenous chemicals, first from the mother, the placenta, and from the developing fetus itself, circulate in very low concentrations, typically in the part-per-trillion to part-per-billion range. Hormones signal when genes need to be active and when to be silent. As complexity builds, the ever-changing mixture of natural hormones ensures normal development; too little or too much leads to disease and pathology. More than a century of biological research has proven that the programming and regulation of life processes require hormones in particular amounts at particular times and, further, that each organ's and tissues' needs change through the life cycle. Early life, especially the fetus and infant, is a period of vulnerability, when any disruption to natural processes may change, sometimes irreversibly, the structure and/or function of a physiological system. The timing of release, in addition to the amount of hormone, is absolutely crucial to normal development. It stands to reason, then, that because EDCs interfere with hormone actions, their exposures during a sensitive developmental period can have both immediate as well as more Introduction to EDCs (December 2014) 27 latent consequences. The timing of exposure is key to understanding which organ or tissue may be affected, as the development of different parts of the body occurs at different rates. Thus, an organ that is developing during the time of the harmful exposure is more likely to be affected than an organ that has already completed development. The outcomes of exposures during vulnerable periods may be physical malformations, functional defects, or both. Consider again the example of DES given to pregnant women, whose female fetuses often had structural malformations of the reproductive tract, together with an increased propensity for rare vaginocervical carcinomas later in life. Another very

real and complex aspect of the windows of vulnerability concept is that the same exposure can have different effects depending on when in development the exposure occurred. For instance, in rodents, first trimester exposure of a fetus to the pesticide chlorpyrifos, a known EDC, can alter thyroid structure and function in the offspring when they become adults, while second trimester exposure to chlorpyrifos can increase insulin levels in the adult offspring. Some disturbances in hormone levels may not cause obvious structural changes, but may still lead to functional changes, disease, or dysfunction, later in life. This concept of windows of vulnerability is referred to variously as the "Fetal basis of adult disease (FeBAD)" or the "Developmental origins of health and disease.

II.

III. THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (DOHAD) DOHaD, also referred to as the "Fetal basis of adult disease" (FeBAD), is based on scientific evidence that the roots of many diseases and dysfunctions occur very early in life, especially the embryo, fetus, infant, and child. For example, under- or over-nutrition of a pregnant woman has an influence on the fetus's propensity to develop metabolic disorders including obesity, diabetes, and others, later in life. This research has since been extended to environmental influences such as cigarette smoking, pollution, and environmental chemicals. Other evidence has shown that the developing germ cells – precursors to the sperm and egg cells of the fetus – are quite vulnerable to disruptions from even low doses of EDCs. More recently, the nervous system, the development of which begins in early gestation and continues well into childhood, has been found to be very sensitive to EDC exposures. Certain cancers, especially reproductive cancers, seem to have their origins in early life. While the manifestation of disease or disorder may not be apparent at birth, following a latent period the results of these exposures become evident, often in adolescence, adulthood or aging. Thus, DOHaD is a key concept in understanding the influence of EDC exposures during these vulnerable periods. 28 HAD)" (Box 1). This field is well accepted by researchers who acknowledge that children are more vulnerable than adults to EDCs because their bodies are still developing. Children are also at greater risk of exposures than adults for a number of reasons including that: 1) they are exposed to many fat-soluble contaminants in breast milk or in formula; 2) they put their hands and objects in their mouth far more often than adults; 3) they live and play close to the ground; and 4) they have greater skin area relative to their body weight than adults allowing for more absorption of chemicals (55). The harm of exposures to children is thus due to differences in the ways they may be exposed, their developmental vulnerability, and a longer life expectancy with a much longer horizon for exposure to manifest as disease. Furthermore, they have limited understanding of danger, and are politically powerless to avoid exposures. While this discussion has focused on the particular vulnerability of the embryo, fetus, infant, and child, every phase of the life cycle, from childhood to adolescence, adulthood, and aging, is sensitive to hormones and EDCs.

Traditional toxicological testing invokes the concept that "the dose makes the poison" (Table 4). The new scientific insights of EDCs suggests that "the timing makes the poison" in considering the vulnerability of the developing organism. III. THRESHOLDS, LOW DOSES, AND THE CONCEPT OF NO SAFE DOSE The assumption that each chemical has a 'safe or acceptable exposure' has led to the generally accepted dogma that every compound has a threshold, and that exposures to levels below that threshold are safe. The 'old science' paradigm on which this conclusion is based emphasizes a carcinogenic/survival index, tests only single pure compounds, ignores mixture effects, and presumes a threshold dosage below which there is no observed adverse effect (NOAEL). In the tests to determine a safe threshold, different concentrations of a single chemical are administered. Toxicity is usually established in a two-year chronic study in rodents (usually adults) that determines the dosage at which one-half of the animals die or develop the target disease (usually a cancer). From this point studies establish the highest dose that has no observable toxicity (again, the endpoint is usually cancer or organ failure). This dosage in turn is divided by an arbitrary 'safety factor', usually 100. For chemicals that have received little testing, an additional factor of 10 (leading to a safety factor of 1000) might be utilized. The definition of 'safe' is extrapolated from these studies of death and dying despite the fact that other, more subtle effects may be induced even at these lower levels. Without actually looking for perturbations in an endpoint that is not as obvious as death, it is not possible to know if hormone levels are being affected, and whether/how that might change Introduction to EDCs (December 2014) 29 the predisposition to develop a disease. Considering that the consequences of some endocrine disorders may not be observed for weeks, months, or years, the inability of toxicological testing to quantify such non-observable outcomes is a serious limitation of this approach to determining risk. The "safe exposure threshold" approach began to be questioned in the 1980s as scientists began to better understand how natural hormones work in the body, how precisely the synthesis and release of hormones is regulated by our endocrine glands and how the body changes during development. (For example, there are periods of life when an individual may normally have no exposure at all to a particular natural hormone, and exposure to an EDC acts upon pathways that would otherwise be completely inactive at that life stage. At these times, even in very low concentrations, any exogenous EDC will exceed the body's natural endogenous hormone levels, which are zero). This led to a call for the development of biologically (vs. hypothetical) based dose-response models that could realistically reflect how the body responds to hormones and chemicals. The development of accurate risk assessments of safety has been hindered by the cost of biological testing in animals. However, the first, and most important, experiment proving that there can be no threshold for EDCs (56) took place in the 1990s. In the red-eared slider turtle, it is the temperature during the mid-trimester of development that determines whether the individual will develop as a male or a female, similar to how the X and Y chromosome

determine sex in humans. With that exception, (sex chromosome vs. temperature), the remaining biological processes of sexual development are remarkably similar between turtles and humans. This makes the turtle a unique biomedical model of sex determination. Importantly, the effect of temperature can be overcome by application of hormones (57) or EDCs (56, 58) to the embryo. To test whether or not low dosages of hormones or EDCs can alter whether an individual becomes a male or a female, 2400 turtle eggs were exposed to an EDC that mimics estrogen's effects during a key developmental period when sex is determined (56). For example, if estrogen, or an estrogenic EDC such as a PCB, is added to eggs that are incubated at a temperature that normally produces only males, all of the offspring will be females. Further, these females will be sterile when they grow up. Using this model, a key experiment was performed demonstrating that extraordinarily low dosages of hormones or EDCs, given at key developmental periods when sex is determined, can permanently change whether an individual becomes a male or a female (56). To understand this, recall that estrogen is a natural hormone that affects an organism at very low concentrations. Therefore, any additional exposure to a synthetic 30 EDC that mimics estrogen's effects may result in levels that by default exceed the threshold for adverse effects in that organism. To test the traditional toxicological hypothesis of safe levels of exposure, a huge study was performed involving more than 2400 eggs (57). What was found was that even the lowest dose of exogenous estradiol increased the proportion of expected females by more than 10% beyond the temperature control. The most striking feature of these studies is that it represented the first evidence that a threshold dose may not exist when an exogenous EDC mimics an endogenous hormone by acting through the same endogenous mechanism. The work with turtles is important for two reasons. First, it puts to rest the argument that it is not possible to determine 'no threshold,' as these studies incontrovertibly prove no threshold. Second, the biological processes of development in this species can be directly extrapolated to all other species, including humans. Since the early work in turtles, there have been many studies showing that even extremely low dosages of EDCs can alter biological outcomes and, importantly, that the effects of low doses cannot be predicted by the effects observed at high doses (54). IV. MIXTURES In a laboratory the emphasis is on rigorous control of the environment, so that elements can be manipulated and outcomes assessed. For example, some work is conducted in homogeneous cultures of a cell line, grown under identical conditions.

IV.

V. SUMMARY OF GAPS BETWEEN MODERN SCIENCE AND REGULATORY POLICY Although consensus is building on how exposures to EDCs are relevant to humans, not all controversies have been resolved. One issue revolves around the difficulty in understanding how very low dose exposures are biologically relevant. This concept is easier to understand in the context of development. There are times in life when there is literally no exposure to a

natural hormone; thus, any exposure to even minute amounts of hormonally active substances will by definition change target cells that are sensitive to hormones. As basic scientists and clinicians with expertise in endocrinology have become increasingly involved in research and practice on EDCs, the evidence for lowdose effects is growing. Nevertheless, there is still a gap between endocrine science and regulatory policy. It is important that decisions about regulation of chemicals be based on the most modern scientific understanding of how hormones act, and how EDCs perturb these actions. Introduction to EDCs (December 2014) 31 from one culture plate to the next. Animal work is conducted in a laboratory with row after row of cages of mice, each genetically identical to the others, with a very specific type of bedding, food, water, light cycle, and controlled temperature. The essence of traditional toxicological methods is the administration of a single, pure chemical in exact dosages, with all other conditions equal to allow comparison of the chemical to a control (placebo) group. However, the world is not like a laboratory. Humans are genetically unique (other than identical twins); they live in very different environments; they migrate to new environments; each person has his/her own dietary and nutritional exposures, etc. Each person is exposed to mixtures of EDCs at various developmental periods – that is, each person has a unique "exposome," the sum of everything to which he or she is exposed. The 'new science' of EDCs recognizes these realities: that exposure in nature is chronic; that EDCs are ubiquitous and global; and that there is bioaccumulation and biomagnification of EDCs up the food chain. Furthermore, with the exception of occupational exposures, it is rare that environmental exposure involves pure compounds. Instead, exposures involve mixtures of compounds, as well as degradation products of single compounds. Thus, modern science must include studies on effects of single compounds, but more importantly, their mixtures, to better approximate the additive or synergistic effects of compounds in the body. There is still some controversy as to whether EDCs exhibit synergistic activity. The heat of that debate stems from the fact that a number of EDCs have a lower potency than natural hormones and, when considered individually, these chemicals may exist in the environment in concentrations believed to be too low to be of concern. However, in the absence of a so-called 'safe dose', these low environmental levels may still have biological actions. Much debate in this area has been based on the old science of extrapolating low-dose effects from high-dose experiments, rather than on real life physiology of hormone actions, or the real-world nature of exposures – the modern paradigm shift that is needed in understanding biological actions of EDCs

Thank you for your consideration.

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